

**REMARKS**

In this Amendment, the specification has been amended as presented hereinabove to reflect the insertion of SEQ ID NO: designators into the appropriate parts of the disclosure to identify the sequences as presented in the accompanying substitute Sequence Listing, filed concomitantly with this Amendment. In addition, changes to correct clerical and/or inadvertent oversights in the specification have been made. No new matter has been added by virtue of the amendments made to the specification. The SEQ ID NO: designators have been added to identify sequences that were originally filed.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached pages are captioned **"Version with Markings to Show Changes Made"**.

Also submitted with this Amendment is a substitute Sequence Listing (pages 1-32); a computer readable form of the substitute Sequence Listing (3.5 inch floppy disk) and a Statement in accordance with 37 C.F.R. §§1.821-1.825 to support the filing and submission of the substitute Sequence Listing.

**AUTHORIZATION**

Should any fees be deemed to be properly assessable in this application for the timely consideration of this Amendment and substitute Sequence Listing submission, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. 13-4500, Order No. 2976-4037. **A duplicate copy of this sheet is attached.**

**CONCLUSION**

In the event that the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is hereby respectfully requested to telephone the applicants' undersigned representative at (212) 415-8751 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

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Date: April 3, 2002

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**Version with Markings to Show Changes Made**

On page 2, the paragraph beginning at line 5 through line 19 has been replaced as follows:

Darier disease, cardiomyopathy, Spinocerebellar ataxia-2, brachydactyly, Mevalonicaciduria, Hyperimmunoglobulinemia D, Noonan syndrome-1, Cardiofaciocutaneous syndrome, spinal muscular atrophy-4, tyrosinemia, phenylketonuria, B-cell non-Hodgkin lymphoma, Ulnar-mammary syndrome, Holt-Oram syndrome, Scapuloperoneal spinal muscular atrophy, alcohol intolerance, MODY, Diabetes mellitus, noninsulin-dependent,2 and diabetes mellitus insulin-dependent (See National Center for Biotechnology Information at the website of: (hypertext transfer protocol, (i.e., http), world wide web, (i.e., www), National Center for Biotechnology Information (ncbi), National Library of Medicine (nlm), National Institutes of Health (NIH), Government (gov)/omim.), [http://www.ncbi.nlm.nih.gov/ornim/].) Although this region appears to contain genes affecting these disorders few genes have been discovered. There is a need in the art for identifying specific genes for such disorders because they are also associated with obesity and lung disease, particularly inflammatory lung disease phenotypes such as Chronic Obstructive Lung Disease (COPD), Adult Respiratory Distress Syndrome (ARDS), and asthma. Identification and characterization of such genetic compositions will make possible the development of effective diagnostics and therapeutic means to treat lung related disorders as well as the other diseases described herein.

On page 4, the section entitled "BRIEF DESCRIPTION OF THE FIGURES" beginning at line 17 through line 30 has been replaced as follows:

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 shows the plot of multipoint LOD score against the map location of the markers along chromosome 12.

Figure 2 depicts the STS content of the 12q23-qter BAC RP11-0702C13 containing Gene 214.

Figures 3A-3C (SEQ ID NOS: 2-3) depict the nucleotide and amino acid sequence of Gene 214a.

Figures 4A-4C (SEQ ID NOS: 4-5) depict the nucleotide and amino acid sequence of Gene 214b.

Figures 5A-5C (SEQ ID NOS: 6-7) depict the nucleotide and amino acid sequence of Gene 214c.

Figures 6A-6D (SEQ ID NOS: 8-9) depict the nucleotide and amino acid sequence of Gene 214d.

Figures 7A-7D (SEQ ID NOS: 10-11) depict the nucleotide and amino acid sequence of Gene 214e.

Figures 8A-8B show a schematic view of the exons of Gene 214a, 214b, 214c, 214d, and 214e and the corresponding single nucleotide polymorphisms.

Figure 9 shows a Northern Analysis of Gene 214.

Figure 10A-10B (SEQ ID NOS: 38-45, respectively, in order of appearance) [depicts] depict the nucleic acid sequence of the [exos] exons of Gene 214.

On page 20, the paragraph beginning at line 18 through line 29 has been replaced as follows:

Alternatively, substantial homology or similarity exists when a nucleic acid or fragment thereof will hybridize, under selective hybridization conditions, to another nucleic acid (or a complementary strand thereof). Selectivity of hybridization exists when hybridization which is substantially more selective than total lack of specificity occurs. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about nine or more nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%. [(See, Kanehisa, [CITE] 1984.)] (See, M. Kanehisa, 1984, Nucleic Acids Res., 12(1 Pt 1):203-13; M. Kanehisa et al., 1984, Nucleic Acids Res., 12(1 Pt 1):149-58; M. Kanehisa et al., 1984, Nucleic Acids Res. 12(1 Pt 1):417-28). The length of homology comparison, as described,

may be over longer stretches, and in certain embodiments will often be over a stretch of at least about 14 nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides.

On page 41, the last paragraph beginning at line 21 through line 30 has been replaced as follows:

1. Map Integration. Various publicly available mapping resources were utilized to identify existing STS markers (Olson et al, (1989), *Science*, 245:1434-1435) in the 12q23-qter region. Resources included the Genome Database (GDB) at the website of: (hypertext transfer protocol, genomedatabase, world wide web.gdb.org/); [http://gdbwww.gdb.org/),] Genethon at the website of: (hypertext transfer protocol, world wide web, genethon-en.html); [(http://www.genethon.fr/genethon\_en.html),] Marshfield Center for Medical Genetics at the website of: (hypertext transfer protocol, world wide web, marshmed.org/genetics/); [(http://www.marshmed.org/genetics/),] the Whitehead Institute Genome Center at the website of: (hypertext transfer protocol, world wide web-genome.wi.mit.edu/); [(http://www-genome.wi.mit.edu/),] GeneMap98, dbSTS and dbEST at the website of: NCBI, (hypertext transfer protocol, world wide web, ncbi.nlm.nih.gov/); [(NCBI, http://www.ncbi.nlm.nih.gov/),] the Sanger Centre at the website of: (hypertext transfer protocol, world wide web.sanger.ac.uk/); [(http://www.sanger.ac.uk/),] and the Stanford Human Genome Center at the website of: (hypertext transfer protocol, world wide web-shgc.stanford.edu/), [(http://www-shgc.stanford.edu/)]. Maps were integrated manually to identify markers mapping to the disorder region. A list of the markers is provided in Table 2.

On page 42, the first paragraph beginning at line 5 through line 15 has been replaced as follows:

2. Marker Development. Sequences for existing STSs were obtained from the GDB, RHDB at the website of the Genome Database, RHDB, (hypertext transfer protocol, world wide web, ebi.ac.uk/RHdb/), [(http://www.ebi.ac.uk/RHdb/)], or NCBI and

were used to pick primer pairs (overgos, See Table 2) for BAC library screening. Novel markers were developed either from publicly available genomic sequences, proprietary cDNA sequences or from sequences derived from BAC insert ends (described below). Primers were chosen using a script that automatically performs vector and repetitive sequence masking using Crossmatch (P. Green, U. of Washington); subsequent primer picking was performed using a customized Filemaker Pro database. Primers for use in PCR-based clone confirmation or radiation hybrid mapping (described below) were chosen using the program Primer3 (Steve Rozen, Helen J. Skaletsky (1996, 1997); Primer3 is available at the website of (hypertext transfer protocol, world wide web, - genome.wi.mit.edu/genomesoftware/other/primer3.html). [[http://www-genome.wi.mit.edu/genome\\_software/other/primer3.html](http://www-genome.wi.mit.edu/genome_software/other/primer3.html)].]

On page 42, Table 2 between lines 15 and 19 has been replaced as follows:

Table 2:

Overgo	Locu s	DNA Type	Gene	Forward Primer	Reverse Primer
B0702C13A1x		BACend		GTAAGTAACAGAATGGACTTTGA (SEQ ID NO: 12)	AGAGAGGAACAGCATCAAAGTC (SEQ ID NO: 13)
A005Q05		EST		CAAACAGGGTCCACCGTGGAAA (SEQ ID NO: 14)	GTGTTTCAGCCACATTCCACG (SEQ ID NO: 15)
Th		Gene	Mucin 8 (MUC8)	ATCCACCGCTAGAAACCCACTC (SEQ ID NO: 16)	GACCATCAACTGATGAGTGGGT (SEQ ID NO: 17)
B0702C13A1y		BACend		TCATGGGGGTGCTTTGACCTTG (SEQ ID NO: 18)	TGGCCTCAAAGGCTCAAGGTCA (SEQ ID NO: 19)

On page 48, the paragraph numbered "7." from lines 24 to 30 has been replaced as follows:

7. BAC Endsequencing. The sequence of BAC insert ends utilized DNA prepared by either of the two methods described above. The ends of BAC clones were sequenced for the purpose of filling gaps in the physical map and for gene discovery information. The following vector primers specific to the BAC vector pBACe3.6 were used to generate endsequence from BAC clones:

pBAC 5'-2 TGT AGG ACT ATA TTG CTC (SEQ ID NO: 20) and  
pBAC 3'-1 CGA CAT TTA GGT GAC ACT (SEQ ID NO: 21).

On page 50, the last paragraph on the page from lines 29 to 31 has been replaced as follows:

The purified DNA fragments were then blunt-ended using T4 DNA polymerase. The healed DNA was then ligated to unique BstXI-linker adapters (5' GTCTTCACCAACGGGG (SEQ ID NO: 22) and 5' GTGGTGAAGAC (SEQ ID NO: 23) in 100-1000 fold molar excess).

On page 64, Table 3 on the page between lines 11 to 15 has been replaced as follows:

Table 3:

Gene	Exon	SSCP Assay	Forward Primer	Reverse Primer
214	A	196_214_A_F_197_214_A_R	GCCCTTAGGGAGAGCAGC (SEQ ID NO: 24)	CCACATCGTGCCTTTGTGTA (SEQ ID NO: 25)
214	B	192_214_B_F_193_214_B_R	CACTGTGTTAAAACGCCTGG (SEQ ID NO: 26)	GTTGGGATTACAGGCACGAG (SEQ ID NO: 27)
214	B	194_214_B_F_195_214_B_R	CAGAAGCAACCCACATGACC (SEQ ID NO: 28)	ACTACAGGTTTGCAACCA (SEQ ID NO: 29)
214	C	626_214_C_F_627_214_C_R	ATGCTCTCTGATGGCTCCT (SEQ ID NO: 30)	AGGGAATGCAGGTGCAAAG (SEQ ID NO: 31)
214	C	628_214_C_F_629_214_C_R	ACTCGGGAAGGAAGGCTCT (SEQ ID NO: 32)	CATACCTTGAGTGACACCG (SEQ ID NO: 33)

On page 64, Table 4 on the page between lines 20 to 25 has been replaced as follows:

Table 4:

Gene	Exon	ForwardPrimer	ForwardSequence	ReversePrimer	ReverseSequence
214	B	MDSeq_15_214_B_F	GACAGTCTGCTCCACATCCA (SEQ ID NO: 34)	MDSeq_15_214_B_R	TGGAGATGAAGTCTTGCTCTTG (SEQ ID NO: 35)
214	C	MDSeq_110_214_C_F	ATATGTTTGCTGGCTTTGGG (SEQ ID NO: 36)	MDSeq_110_214_C_R	CCCAGGCTGTGTCTCTTA (SEQ ID NO: 37)

On page 65, Table 5 on the page between lines 10 to 13 has been replaced as follows:

Table 5:

Exon	Reference Sequence	PMP	Intron/Exon	Location
B	ACTACAGGTTTGCACCACCA <u>T</u> GTCTCTGCTAATTTTTTTTTT (SEQ ID NO: 46)	A>G (SEQ ID NO: 47)	Intron	6684
B	TGTGCACTCTTGGGCATACGCCTAGGAGTGGAAGTCTG (SEQ ID NO: 48)	C>T (SEQ ID NO: 49)	3'UTR	6991
C	GGGCTCTGCGCCACCTCAACCCAGGCGTTTGTTCGCGAG (SEQ ID NO: 50)	C>T (SEQ ID NO: 51)	Intron	3176